Original Article

Transcutaneous Bilirubinometry in Preterm and Term Newborn Infants before and during Phototherapy

Mitra Radfar MD[1], Mozhgan Hashemieh MD•[1], Fariba Shirvani MD[1], Ramin Madani MD[1]

Abstract

Introduction: To evaluate the accuracy of transcutaneous bilirubin measurement in a large population of newborn infants, before and during the phototherapy.

Patients and Methods: A single Bilicheck instrument was used for transcutaneous measurements. A photo-opaque patch was positioned over the measurement site prior to starting phototherapy. Transcutaneous bilirubinometry was conducted on an unpatched area of the forehead skin and on the nearby site covered by the photo-opaque patch. Readings were obtained from patched and unpatched areas and simultaneous total serum bilirubin concentrations were compared.

Results: We studied 134 term and 36 preterm newborns. Pre-phototherapy measurements showed a strong correlation (r: 0.929, $P < 0.001$, Limit of agreement: -1.8 to 3.1) between Bilicheck and serum bilirubin readings. Post-phototherapy correlation between Bilicheck and serum bilirubin readings was (r: 0.921, $P < 0.001$, LOA: -1.8 to 2.8) among term and (r: 0.887, $P = 0.001$, LOA: -1.4 to 2.7) among preterm neonates in patched areas. These correlations were (r: 0.666, $P < 0.001$, LOA: -1.7 to 7.3) among term and (r: 0.756, $P < 0.001$, LOA: -0.5 to 5.3) preterm neonates post-phototherapy in unpatched areas.

Conclusion: BiliCheck can be safely used for the evaluation of bilirubin levels in preterm and term newborn infants under phototherapy. BiliCheck is slightly less reliable among preterm newborns.

Keywords: Icterus, Iran, newborn, phototherapy, preterm, transcutaneous bilirubinometry

Introduction

N eonatal jaundice is one of the most common complications of neonates, especially among the Asian races. A majority of neonates develop visible jaundice within the first few days of birth and the evaluation of its severity is an important aspect in its management.[1–6] Visual inspection is the most common method of detection for hyperbilirubinemia. However, assessment of the laboratory total serum bilirubin level, which is an invasive, stressful and time-consuming procedure with significant interlaboratory and intralaboratory variability, is a routine procedure to confirm it.[7,8] Although blood can be sampled routinely from neonates, it is painful and might cause local infection.[8] Therefore, an accurate and noninvasive method of monitoring of jaundice in such neonates would be desirable [8]

To address this need for a noninvasive method of evaluating the neonatal jaundice, transcutaneous bilirubinometry (TCB) was introduced by Yamanouchi, et al.[9] as an easy, safe and convenient method for measuring the severity of jaundice. Transcutaneous bilirubinometry is a noninvasive and cost effective method, which utilizes reflectance photometry or transcutaneous colorimetry as an immediate estimate of total serum bilirubin (TSB) levels and reduces the number of invasive blood samplings.[8,9] In recent

Authors' affiliations: [1]Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
•**Corresponding author and reprints:** Mozhgan Hashemieh MD, Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Shahid Madani Street, Tehran, Iran. Cell Phone: +98-912-1015080, E-mail: mozhganhashemieh@gmail.com.
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years, technological improvements have provided new devices for noninvasive bilirubin assay, and transcutaneous bilirubinometry is now becoming a widespread method.[10]

Among these devices, Bilicheck (SpectRx, Inc, Norcross [GA], US) has been reported as an accurate and useful screening method.[10,11] Bilicheck measures optical densities attributed to bilirubin and other skin pigments,[10,11] and its usefulness in neonatal jaundice has been well tested in various groups of term or near-term,[12–14] preterm,[15,16] sick,[17] and in multi-racial neonates.[18–20]

Phototherapy is a widely accepted treatment for neonatal indirect hyperbilirubinemia.[10] It has been reported that phototherapy adversely affects the correlation between TCB and blood measurements[6,21] however, it is well known that the blanching effect of the light exposure only happens in exposed areas, while covered sites remain icteric.[10] Therefore, the use of patching improve the reliability of TCB.

Yasuda, et al.[22] reported that the correlation between TCB and TSB was similar among preterm and term neonates. However, Namba and Kitajima reported that the accuracy and reliability of TCB versus TSB diminishes in neonates with birth weights < 1000 g or gestational ages < 28 weeks, compared with results in larger, and more mature preterm neonates.[8,23] Race, as assessed by the skin color score, birth weight, gestational age, and postnatal age don't seem to affect the Bilicheck device.[24]

Although few studies about the accuracy of transcutaneous bilirubinometry have been performed among the Iranian population,[8,20,25,26] to our knowledge, there is not one single study addressing the use of this method both among term and preterm newborns, as well as in patched and unpatched conditions. This prospective cohort study was designed to evaluate the accuracy

of TCB measurement on exposed and unexposed skin areas during phototherapy among preterm and term Iranian neonates with the aim of reducing painful blood sampling for serum bilirubin measurements.

Patients and Methods

This prospective study was conducted in the neonatal ward of Imam Hossein Medical Center, Tehran, Iran, a tertiary referral centre with approximately 3100 deliveries a year, between June 2012 and October 2012. We included both preterm (under 37 weeks of gestation) and term neonates in our study. The institutional review board of Shahid Beheshti University of Medical Sciences approved this study, which was considered a noninvasive one. Parents of newborns gave written informed consent. The inclusion criteria were all neonates with indirect hyperbilirubinemia who needed phototherapy without considering the gestational age.

Exclusion criteria were perinatal infections, cholestasis, and major congenital malformations. The decision to use phototherapy was made by the attending neonatologist based on criteria by American Academy of Pediatrics (AAP). No prophylactic intervention for hyperbilirubinemia was used. All babies were naked and diapered to allow maximum skin exposure to phototherapy, while environmental lighting was constant during the study period. Phototherapy was given using standard phototherapy units placed 40 cm above the neonate; and was interrupted when there was a need for feeding breaks. Eye protection was used during treatment, and babies were turned every 6 hours from prone to supine position and vice versa to achieve uniform exposure to the light.

A single Bilicheck instrument was used, which was calibrated everyday with a disposable tip according to the manufacturer's recommendations. A photo-opaque patch 2.5 cm in diameter (BiliEclipse TM Phototherapy Protective Patch, Respironics, Murrysville, PA, USA) was placed over the measurement site prior to the phototherapy. TCB was measured on an unpatched area of the forehead skin (UTCB) and on the nearby site covered by the photo-opaque patch (PTCB). Transcutaneous and blood assays were performed with a maximum interval of at most 30 minutes between them after at least 6 hours of phototherapy. After blood samples were taken, capillary tubes were protected from light exposure and total serum bilirubin (TSB) was measured using a direct spectrophotometer. The TCB was obtained from patched and unpatched areas and the simultaneous TSB concentrations were recorded in a pre-designed information sheet for each patient.

Statistical analysis was performed using SPSS statistical software version 20 (Armonk, NY: IBM Corp). We used the Spearman nonparametric regression to estimate the relationship between the TSB and TCB. The regression equation was expressed with the 95% confidence interval for estimates of the slope and intercept. Mountain plots were used to visualize the agreement between the TSB and PTCB or UTCB. A *P*-value less than 0.05 was considered to be statistically significant.

Sample size of 169 patients was calculated to detect a difference of 5%, with 85% power between methods of neonatal jaundice measurement. Based on a previous study,[10] the standard deviation for the mean difference between TSB and PTCB methods was 3.1 mg/dL while the mean difference between TSB and UTCB methods was 3.0 mg/dL.

Results

We studied 170 newborn infants with a mean age 3.8 ± 1.4 days, gestational age of 37 ± 2.0 weeks and a mean birth weight 2815 ± 632 grams at birth (Table 1).

Study population included 36 preterm (21.2%) and 134 term (78.8%) newborns. There was a slight higher prevalence of males (52.4%). The incidence of caesarean section was 68.5%.

Mean TSB (11.9 ± 3.3 mg/dL) and UTCB (11.2 ± 3.4 mg/dL) readings were statistically different before phototherapy. The mean pre phototherapy difference between TSB and UTCB was 0.6 ± 1.3 mg/dL (95% CI: 0.5 to 0.8, $P < 0.001$). But these measurements showed a strong correlation of (r: 0.929, $P < 0.001$, LOA: -1.8 to 3.1) (Table 2) (Figure 1). This correlation was (r: 0.935, $P < 0.001$, LOA: -1.7 to 3.1) among preterm and (r: 0.929, $P < 0.001$, LOA: -1.9 to 3.1) among term newborns (Table 2) (Figure 1).

The mean post-phototherapy TSB (9.5 ± 2.8 mg/dL) and PTCB (9.0 ± 3.0 mg/dL) readings were statistically significantly different. The mean post phototherapy difference between TSB and PTCB was 0.5 ± 1.2 mg/dL (95% CI: 0.3 to 0.7, $P < 0.001$). These measurements showed a strong correlation of (r: 0.922, $P < 0.001$, LOA: 1.8 to 2.8) (Table 3) (Figure 2). This correlation was (r: 0.921, $P < 0.001$, LOA: -1.8 to 2.8) among term and (r: 0.887, $P = 0.001$, LOA: -1.4 to 2.7) among preterm infants (Table 3) (Figure 2).

The mean post-phototherapy TSB (9.5 ± 2.8 mg/dL) and UTCB (6.8 ± 2.8 mg/dL) readings were different post-phototherapy. These measurements showed a correlation of (r: 0.694, $P < 0.001$, LOA: -1.5 to 7.0) (Table 4) (Figure 3). This correlation was (r: 0.666, $P < 0.001$, LOA: -1.7 to 7.3) among term and (r: 0.756, $P < 0.001$, LOA: -0.5 to 5.3) among preterm infants (Table 4) (Figure 3).

Discussion

Previous studies have suggested that transcutaneous measurement of bilirubin is useful as a screening device for neonatal hyperbilirubinemia.[10,27] Bilicheck is a relatively newer device with inbuilt algorithms for correcting the influence of skin pigments other than bilirubin, which is claimed to be more accurate than older devices.[10]

Accuracy and precision of transcutaneous measurements using Bilicheck have been found to be comparable to those of TSB measurements in different studies,[10,27,28] but the effect of gestational age on TCB measurement still needs to be further studied. Although, a review by Carceller-Blanchard does not discourage the use of TCB in preterm infants.[29]

We found a strong correlation between the Bilicheck readings and TSB readings before phototherapy. This is a further confirmation of earlier studies which have indicated transcutaneous bilirubinometry accuracy in reflecting the plasma bilirubin concentration among both full-term and preterm infants.[2,4,5,7,8,10] This finding shows that Bilicheck can be used as a relatively reliable screening method for detecting significant jaundice that might need further evaluation by other methods.

After phototherapy and without using a patch, such a correlation still exists, but to a significantly lesser extent; correlation is significantly weaker and the points are widely dispersed, in line with findings in other studies, both among term and preterm patients.[6,10,30]

Table 1. Demographic findings of study participants.

Parameter	Value
Gestational age (Weeks)	
Mean ± SD	37 ± 2
Median (range)	38 (28 to 40)
Age (days)	
Mean ± SD	3.8 ± 1.4
Median (range)	4 (1 to 8)
Weight (gr)	
Mean ± SD	2815 ± 632
Median (range)	2900 (1100 to 4300)
Gender	
F	81 (48%)
M	89 (52%)
Gestational age	
Term	134 (79%)
Preterm	36 (21%)
Duration of phototherapy (Hours)	
Mean ± SD	10 ± 5
Median (range)	8 (2 to 30)
M.BG*	
A	40 (24%)
AB	30 (18%)
B	52 (31%)
O	48 (28%)
M.Rh**	
Positive	138 (81%)
Negative	32 (19%)
N.BG*	
A	58 (34%)
AB	15 (9%)
B	57 (34%)
O	40 (24%)
N.Rh***	
Positive	152 (89%)
Negative	18 (11%)
Hx (Positive sibling history)	
Yes	13 (8%)
No	157 (92%)
Nutrition	
Breast Milk	148 (87%)
Formula	5 (3%)
NPO	17 (10%)
G6PD	
Sufficient	163 (96%)
Deficient	7 (4%)

Results are presented as mean ± SD, Median (Range) and N (%); *Mother blood group; **Mother Rh; ***Newborn blood group; ****Newborn Rh

Table 2. Pre-phototherapy correlation, intraclass correlation coefficient and limit of agreement between UTCB and TSB readings

| | Total | Gestational Age | |
		Term	Preterm
r	0.929	0.929	0.935
ICC	0.912	0.912	0.898
Mean Δ ± SD	0.6 ± 1.3	0.6 ± 1.3	0.7 ± 1.2
Δ 95% CI	0.5 to 0.8	0.4 to 0.9	0.3 to 1.1
Range Δ	-4 to 3	-4 to 3	-2 to 3
P-value	< 0.001	< 0.001	0.002
95%LOA	-1.8 to 3.1	-1.9 to 3.1	-1.7 to 3.1
ICC: Intra-class correlation coefficient; LOA: Limit of Agreement			
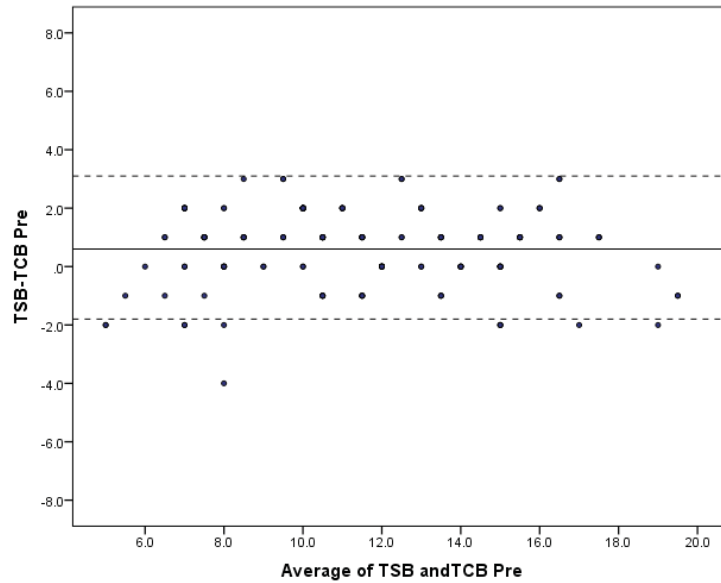
Figure 1. Bland Altman plot demonstrate the agreement of pre-phototherapy measurements using TSB and TCB in unpatched areas.
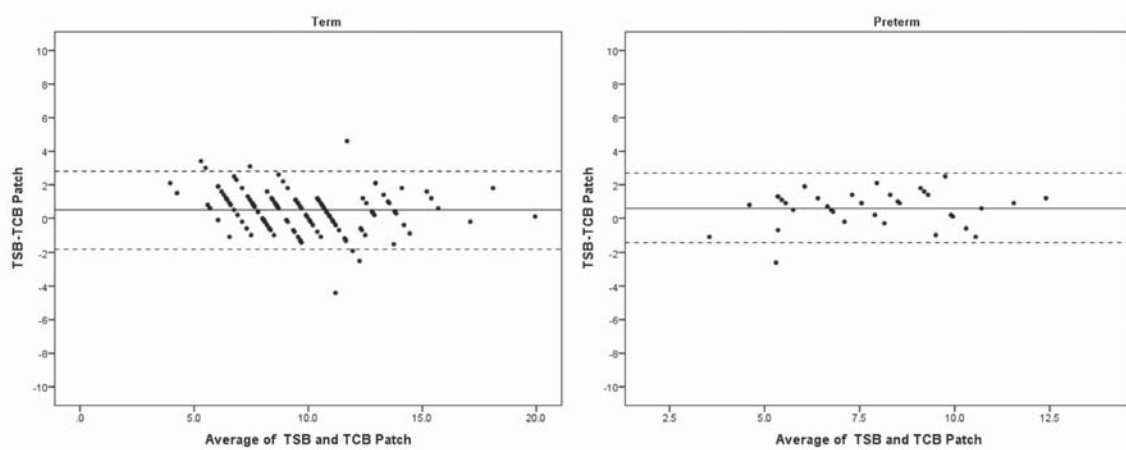
Figure 2. Bland Altman plot demonstrate the agreement of post-phototherapy measurements using TSB and TCB in patched areas considering the gestational age.

This finding indicates that the usefulness of Bilicheck in a clinical situation after using phototherapy is limited because of the wide dispersal of the values when it is used for reading in an unpatched area.

On the other hand, the correlation observed in the patched area unexposed to phototherapy showed a stronger relationship than that of exposed areas with correlations comparable to correlations found with TSB before the phototherapy both among term and preterm newborns. The slight decrease in correlation of Bilicheck readings and TSB after phototherapy in unexposed areas compared with the correlation found before the phototherapy might be due to the equilibration process being delayed with regard to the skin.[10] It should be noted that this correlation was still strong among preterm newborns; it was slightly weaker than the cor-

Table 3. Post-phototherapy correlation, intraclass correlation coefficient and limit of agreement between PTCB and TSB readings
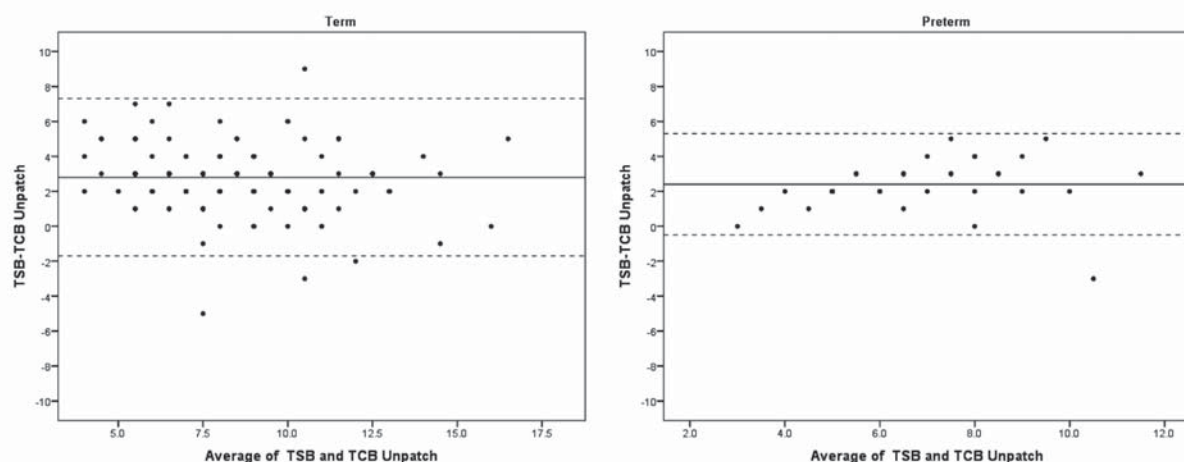
| | Total | Gestational age | |
		Term	Preterm
r	0.922	0.921	0.887
ICC	0.906	0.906	0.854
Mean Δ ± SD	0.5 ± 1.2	0.5 ± 1.2	0.6 ± 1
Δ 95% CI	0.3 to 0.7	0.3 to 0.7	0.3 to 1
Range Δ	-4.4 to 4.6	-4.4 to 4.6	-2.6 to 2.5
P-value	< 0.001	< 0.001	0.001
95% LOA	-1.8 to 2.8	-1.8 to 2.8	-1.4 to 2.7
ICC: Intraclass correlation coefficient; LOA: Limit of Agreement			

Table 4. Post-phototherapy correlation, intraclass correlation coefficient and limit of agreement between UTCB and TSB readings

| | Pre | Gestational age | |
		Term	Preterm
r	0.694	0.666	0.756
ICC	0.466	0.443	461
Mean Δ ± SD	2.7 ± 2.2	2.8 ± 2.3	2.4 ± 1.5
Δ 95% CI	2.4 to 3.1	2.4 to 3.2	1.9 to 2.9
Range Δ	-5 to 14	-5 to 14	-3 to 5
P-value	< 0.001	< 0.001	< 0.001
95% LOA	-1.5 to 7	-1.7 to 7.3	-0.5 to 5.3
ICC: Intraclass correlation coefficient; LOA: Limit of Agreement			

Figure 3. Bland Altman plot demonstrate the agreement of post-phototherapy measurements using TSB and TCB in unpatched areas considering the gestational age.

relation found among term newborns. Considering more serious ramifications of poorly managed icterus among preterm newborns compared to term neonates, it might be concluded that Bilicheck should be used with more caution among these patients, particularly in those preterm newborns with other complications, which might cause more serious outcomes in the case of a not accurately controlled icterus. Therefore, usefulness of Bilicheck during phototherapy even after patching for determining whether exposure can be terminated in this group of preterm newborns is likely to be limited.

There were a few limitations in our study. First, we did not account for the duration of phototherapy to evaluate the accuracy of TCB measurements. A previous study indicates that the cor-relation between TCB and TSB measurements in exposed and unexposed skin areas is affected by the duration of phototherapy secondary to the bleaching effect.[31]

Secondly, it has been reported in a previous study,[30] the correlation between transcutaneous and TSB readings could be affected by high transcutaneous values (> 11 mg/ dL). In the present study, we did not observe a significant change in the correlations when comparing those patients with readings of higher than 11 mg/dL with other neonates. Because more than 90% of the preterm neonates in the present study had TSB < 11 mg/dL, we assumed that the result was not affected by the TSB values.

In conclusion, based on our findings, we conclude that transcutaneous measurements on the forehead by Bilicheck after patch-

ing can be a useful assay to monitor bilirubin levels in both preterm and term neonates receiving phototherapy with slightly less reliability among preterm newborns. Considering more serious ramifications of poorly managed icterus among preterm newborns compared to term neonates, it might be concluded that Bilicheck should be used with more caution in preterm newborns with other complications, which might cause more serious outcomes in the case of a not accurately controlled icterus.

Conflict of interest

None of the authors have any conflict of interest with the subject matter of the present study.

References

1. Tan KL. Glucose-6-phosphate dehydrogenase status and neonatal jaundice. *Arch Dis Child*. 1981; 56(11): 874 – 877.
2. Osborn LM, Reiff MI, Bolus R. Jaundice in the full-term neonate. *Pediatrics*. 1984; 73(4): 520 – 525.
3. Bhutani VK, Stark AR, Lazzeroni LC, Poland R, Gourley GR, Kazmierczak S, et al. Predischarge screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy. *J Pediatr*. 2013; 162(3): 477 – 482.
4. Keren R, Tremont K, Luan X, Cnaan A. Visual assessment of jaundice in term and late preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2009; 94(5): F317 – F322.
5. Nagar G, Vandermeer B, Campbell S, Kumar M. Reliability of transcutaneous bilirubin devices in preterm infants: A systematic review. *Pediatrics*. 2013; 132(5): 871 – 881.
6. Tan KL, Dong F. Transcutaneous bilirubinometry during and after phototherapy. *Acta Paediatr*. 2003; 92(3): 327 – 331.
7. Neocleous C, Adramerina A, Limnaios S, Symeonidis S, Spanou C, Malakozi M, et al. A comparison between transcutaneous and total serum bilirubin in healthy-term greek neonates with clinicaljaundice. *Prague Med Rep*. 2014; 115(1-2): 33 – 42.
8. Sajjadian N, Shajari H, Saalehi Z, Esphahani F, Alizadeh Taheri P. Transcutaneous bilirubin measurement in preterm neonates. *Acta Med Iran*. 2012; 50(11): 765 – 770.
9. Yamanouchi I, Yamauchi Y, Igarashi I. Transcutaneous bilirubinometry: Preliminary studies of noninvasive transcutaneous bilirubin meter in the Okayama National Hospital. *Pediatrics*. 1980; 65(2): 195 – 202.
10. Zecca E, Barone G, De Luca D, Marra R, Tiberi E, Romagnoli C. Skin bilirubin measurement during phototherapy in preterm and term newborn infants. *Early Hum Dev*. 2009; 85(8): 537 – 540.
11. de Luca D, Zecca E, de Turris P, Barbato G, Marras M, Romagnoli C. Using BiliCheck for preterm neonates in a sub-intensive unit: diagnostic usefulness and suitability. *Early Hum Dev*. 2007; 83(5): 313 – 317.
12. Szabo P, Wolf M, Bucher HU, Haensse D, Fauchère JC, Arlettaz R. Assessment of jaundice in preterm neonates: comparison between clinical assessment, two transcutaneousbilirubinometers and serum bilirubin values. *Acta Paediatr*. 2004; 93(11): 1491 – 1495.
13. Samanta S, Tan M, Kissack C, Nayak S, Chittick R, Yoxall CW. The value of Bilicheck as a screening tool for neonatal jaundice in term and near-term babies. *Acta Paediatr*. 2004; 93(11): 1486 – 1490.
14. Robertson A, Kazmierczak S, Vos P. Improved transcutaneous bilirubinometry: comparison of SpectR(X) BiliCheck and Minolta Jaundice Meter JM-102 for estimating total serum bilirubin in a normal newborn population. *J Perinatol*. 2002; 22(1): 12 – 14.
15. Willems WA, van den Berg LM, de Wit H, Molendijk A. Transcutaneous bilirubinometry with the Bilicheck in very premature newborns. *J Matern Fetal Neonatal Med*. 2004; 16(4): 209 – 214.
16. Knüpfer M, Pulzer F, Braun L, Heilmann A, Robel-Tillig E, Vogtmann C. Transcutaneous bilirubinometry in preterm infants. *Acta Paediatr*. 2001; 90(8): 899 – 903.
17. Ebbesen F, Rasmussen LM, Wimberley PD. A new transcutaneous bilirubinometer, BiliCheck, used in the neonatal intensive care unit and the maternity ward. *Acta Paediatr*. 2002; 91(2): 203 – 211.
18. Rubaltelli FF, Gourley GR, Loskamp N, Modi N, Roth-Kleiner M, Sender A, et al. Transcutaneous bilirubin measurement: a multicenter evaluation of a new device. *Pediatrics*. 2001; 107(6): 1264 – 1271.
19. Ho EY, Lee SY, Chow CB, Chung JW. BiliCheck transcutaneous bilirubinometer: a screening tool for neonatal jaundice in the Chinese population. *Hong Kong Med J*. 2006; 12(2): 99 – 102.
20. Hemmati F, Kiyani Rad NA. The value of bilicheck® as a screening tool for neonatal jaundice in the South of Iran. *Iran J Med Sci*. 2013; 38(2): 122 – 128.
21. Yamauchi Y, Yamanouchi I. Transcutaneous bilirubinometry. Effect of irradiation on the skin bilirubin index. *Biol Neonate*. 1988; 54(6): 314 – 319.
22. Yasuda S, Itoh S, Isobe K, Yonetani M, Nakamura H, Nakamura M, et al. New transcutaneous jaundice device with two optical paths. *J Perinat Med*. 2003; 31(1): 81 – 88.
23. Namba F, Kitajima H. Utility of a new transcutaneous jaundice device with two optical paths in premature infants. *Pediatr Int*. 2007; 49(4): 497 – 501.
24. Kaynak-Türkmen M, Aydoğdu SA, Gökbulut C, Yenisey C, Söz O, Cetinkaya-Cakmak B. Transcutaneous measurement of bilirubin in Turkish newborns: comparison with total serum bilirubin. *Turk J Pediatr*. 2011; 53(1): 67 – 74.
25. Mansouri M, Mahmoodnejad A, Taghizadeh Sarvestani R, Gharibi F. A Comparison between Transcutaneous Bilirubin (TcB) and Total Serum Bilirubin (TSB) Measurements in Term Neonates. *Int J Pediatr*. 2015; 3(1): 633 – 641.
26. Mussavi M, Niknafs P, Bijari B. Determining the correlation and accuracy of three methods of measuring neonatal bilirubin concentration. *Iran J Pediatr*. 2013; 23(3): 333 – 339.
27. Bhutani VK, Gourley GR, Adler S, Kreamer B, Dalin C, Johnson LH. Noninvasive measurement of total serum bilirubin in a multiracial predischarge newborn population to assessthe risk of severe hyperbilirubinemia. *Pediatrics*. 2000; 106(2): E17.
28. Rubaltelli FF, Gourley GR, Loskamp N, Modi N, Roth-Kleiner M, Sender A, et al. Transcutaneous bilirubin measurement: a multicenter evaluation of a new device. *Pediatrics*. 2001; 107(6): 1264 – 1271.
29. Carceller-Blanchard A, Cousineau J, Delvin EE. Point of care testing: transcutaneous bilirubinometry in neonates. *Clin Biochem*. 2009; 42(3): 143 – 149.
30. Nanjundaswamy S, Petrova A, Mehta R, Hegyi T. Transcutaneous bilirubinometry in preterm infants receiving phototherapy. *Am J Perinatol*. 2005; 22(3): 127 – 131.
31. Ozkan H, Oren H, Duman N, Duman M. Dermal bilirubin kinetics during phototherapy in term neonates. *Acta Paediatr*. 2003; 92(5): 577 – 581.